REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Status of Claims

Claims 1, 3, 4, and 6-10 are pending in the application. Claims 1, 3, 4, and 6-10 have been rejected. Claims 1, 3, and 4 have been amended.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

In the Office Action dated October 19, 2006, the Examiner rejected claims 1, 3, 4, and 6-10 under 35 U.S.C. § 103(a), as being allegedly unpatentable over Mao. The Examiner alleged that Mao disclosed: (a) biodegradable medical implant devices that incorporate 1-65% active agent; (b) that any antipsychotic drugs (e.g. clozapine, haloperidol, and risperidone) can be used; and (c) use of lactic acid copolymers. The Examiner alleged that "The difference... between Mao and the instant claims is [only] the amount of the haloperidol" (October 19, 2006 Office Action page 3, first full paragraph). Therefore, Examiner alleged that it would have been obvious to modify the implant of Mao to arrive at the implants claimed in the subject claims.

In a Response dated March 8, 2007, Applicants pointed out to the Examiner that (a) the polymers of Mao differ from those of the present invention in that the polymers of Mao contain a phosphate ester linkage, which is not present in either polylactide or lactide-co-glycolide copolymers; and (b) the phosphate ester materially changes the basic characteristics of thereof, e.g. the degradation pattern and ability to incorporate an active compound into the polymers.

In an Advisory Action dated April 17, 2007, the Examiner alleged that the claim language "consisting essentially of" does not exclude the device of Mao because the device of Mao "is biodegradable, non-toxic and releases antipsychotic drug, haloperidol, when

present." Further, the Examiner alleged that "the claimed invention does not specifically claim or un-claim modified or unmodified lactide or glycolide"; and the subject specification does not make clear what Applicants regard as constituting a material change in the basic and novel characteristics of the invention.

In response, in order to expedite prosecution and without agreeing to the correctness of the rejection, amended claim 1 is directed to a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer ***consisting essentially of*** polylactide or lactide-co-glycolide copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation. Amended claim 4 is directed to a method of producing an individual, surgically implantable implant which is surgically implanted underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising: (a) dissolving haloperidol and a biodegradable polymer ***consisting essentially of*** polylactide or lactide-co-glycolide copolymer in acetone; (b) solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and (c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation.

By contrast, the polymer in the implants of Mao does not consist essentially of polylactide or lactide-co-glycolide copolymer. Rather, as described in more detail hereinbelow, (a) the polymer of Mao contains phosphate ester linkages; and (b) the presence of phosphate ester linkages in the polymer of Mao alters materially the basic and novel characteristics of the invention; namely, the release rate of the implants.

The subject specification shows that release rate of the implants constitutes a basic characteristic of the claimed implants

The subject specification states:

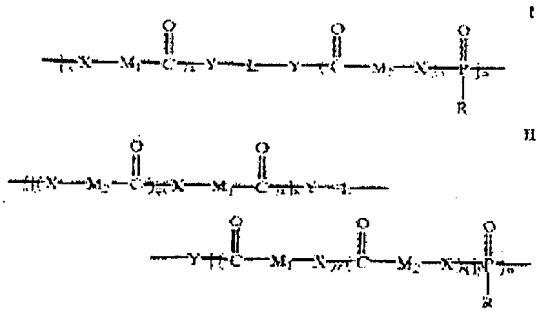
> "The surgically implantable preparations of the present invention are designed to last for months to years" (subject specification page 7, lines 33-34).
>
> "Haloperidol released from the bioerodible implant of the present invention maintains its bioactivity and is delivered at steady state concentrations to the patients for periods of five months or more" (page 13, lines 11-15).

Thus, the subject specification clearly shows that Applicants consider release rate of the implants to constitute a basic characteristic of the claimed implants. In view of this teaching of the subject specification, the basic characteristics of polymer of Mao are materially altered from the claimed implants of the subject invention. Accordingly, the polymer of Mao is excluded by the phrase "consisting essentially of polylactide or lactide-co-glycolide copolymer" in the subject claims.

For the sake of completeness, Applicants now reproduce the evidence that (a) the polymers of Mao differ from those of the present invention in that the polymers of Mao contain a phosphate ester linkage, which is not present in either polylactide or lactide-co-glycolide copolymers; and (b) the phosphate ester linkages materially change the degradation pattern of the implants.

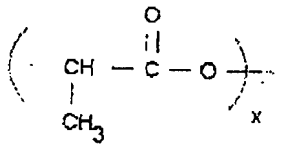
Polymers of Mao differ from those of the present invention in the presence of a phosphate ester linkage

The polymers of Mao have 1 of the following formulas:



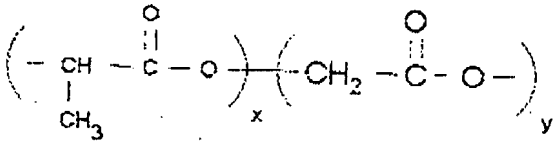
As clearly depicted on the right side of each of the above structures, these polymers contain phosphate esters.

By contrast, polylactide and lactide-co-glycolide copolymers of the subject invention do not contain a phosphate linkage. Polylactide polymers have the formula:



Lactide-co-glycolide copolymers have the formula:

$$[OCH(CH_3)CO]_x[OCH_2CO]_y$$



No phosphate is present in either of the above formulas.

Further, the alleged disclosure of polylactide and lactide-co-glycolide copolymers in columns 12-13 of Mao is limited, as clearly stated in column 12, line 50 of Mao, to the use of polylactide and lactide-co-glycolide copolymers as reagents ("prepolymers") for use in step (b) of the synthesis reaction described in column 11, lines 44-55 of Mao. The purpose of step (b) is to create "interconnecting phosphorylated units" (column 13, lines 36-37). The cited passage does not disclose or contemplate the use of the unmodified prepolymers.

Accordingly, the disclosure of Mao teaches nothing about polymers that do not contain a phosphate moiety; e.g. polymers of the present invention.

The phosphate ester linkages of Mao materially change the degradation pattern of the implants

Further, Mao discloses that the phosphate linkages affect the release rate of the polymers disclosed therein:

> "The polymers of formulas I and II are usually characterized by a release rate of the biologically active substance *in vivo* that is controlled at least in part as a function of hydrolysis of the phosphoester bond of the polymer during biodegradation" (column 14, lines 25-36; emphasis added).

Thus, Mao taught that the phosphate moieties present in the implants disclosed therein affect the drug release rate.

Thus, in view of the teaching of the subject specification that the release rate of the claimed implants constitutes a basic characteristic of the claimed invention, as described hereinabove, the polymer of Mao is materially altered from the claimed implants in its basic characteristics. Accordingly, the polymer of Mao is excluded by the phrase "consisting essentially of polylactide or lactide-co-glycolide copolymer" in the subject claims, thus distinguishing the polymers of Mao from those of the present invention

Mao teaches against removal of the phosphate group

Further, Mao teaches against removal of the phosphate group, by teaching that the phosphate group is critical for the biological functionality.

For example, Mao disclosed in column 14, lines 25-36 that the phosphate linkages affect the release rate of the polymers disclosed therein, as quoted hereinabove.

Further, Mao indicates that the presence of the phosphate group confers ability to incorporate an active compound into the polymers disclosed therein:

> "Additionally, the biologically active substance to be released may be conjugated to the phosphorus sidechain R' to form a pendant drug delivery system" (column 14, lines 36-38).

In summary, Mao taught that the phosphate moieties present in the implants disclosed therein are important both in incorporation of a drug into the polymer and in determining the drug release rate. Thus, since Mao discloses that the phosphate group is central and critical to Mao's disclosure, a person skilled in the art would not remove the phosphate from the polymers of Mao and/or replace it with another moiety. Doing so would completely alter the polymers and resulting implants from the entire disclosure of the invention. Clearly, Mao further teaches against removing the phosphate moieties from the polymers of Mao, thus providing yet another reason why the implants of the present invention are not obvious in view of Mao.

Unexpected properties of the 20-40% range

As mentioned hereinabove, the Examiner alleged that "The difference... between Mao and the instant claims is [only] the amount of the haloperidol" (page 3, first full paragraph of the October 19, 2006 Office Action). Therefore, Examiner alleged that it would have been obvious to modify the 1-65% active agent range disclosed in Mao to arrive at the implants of the present invention, which contain 20-40% haloperidol.

Applicants respectfully traverse the rejection. In making the above allegation, the Examiner has ignored objective indicia of non-obviousness; namely, the decreasing release rate with increasing drug percentage; as disclosed in the subject specification:

> "Haloperidol concentrations preferably range from about 20% to about 40% in the delivery system depending upon the release period. Inclusion of haloperidol in the drug delivery system actually increases the stability of the drug delivery system. Thus, the higher the concentration of haloperidol, the more extended the period of release" (page 9, lines 7-12).

The above surprising property of implants of the present invention was not disclosed or suggested for any of the implants of Mao, thus providing yet another reason why the

implants of the present invention differ from those of Mao and are not obvious in view of Mao.

Melt processing and compression molding

As mentioned hereinabove, the Examiner alleged that Mao disclosed preparation of biodegradable implants by melt processing or by compression molding.

Applicants respectfully assert that Examiner's allegation is irrelevant to the subject claims. Claim 4 recites a method that comprises both solvent casting and compression molding. "Melt processing" is a completely distinct process from solvent casting. Thus, the alleged disclosure cited by the Examiner is irrelevant to the subject claims.

This additional difference between the claimed implants and those of Mao provides yet another reason why the implants of the present invention differ from those of Mao and are not obvious in view of Mao.

Superior steady-state release properties of implants of the present invention

Further, as demonstrated in the subject specification, implants of the present invention exhibit steady-state release for 5 months or more:

> "Haloperidol released from the biocrodible implant of the present invention maintains its bioactivity and is delivered at steady state concentrations to the patients for periods of five months or more" (p. 13, lines 13-16).

This additional difference between the claimed implants and those of Mao was not disclosed or suggested for any of the implants of Mao, thus providing yet another reason why the implants of the present invention differ from those of Mao and are not obvious in view of Mao.

Removability of implants of the present invention

Further, as demonstrated in the subject specification, implants of the present invention are removable, as demonstrated by reversal of *in vivo* effects on locomotion:

> "After apomorphine challenge, animals that had control implants traveled a mean of 4721 ± 476 cm, while those with haloperidol containing implants traveled a mean of 8531 ± 2536 cm. Therefore, following removal of implants and exposure to apomorphine, mice that had haloperidol implants traveled more distance than control mice ($p<0.02$)" (p. 11, lines 8-11).

This additional difference between the claimed implants and those of Mao was not disclosed or suggested for any of the implants of Mao, thus providing yet another reason why the implants of the present invention differ from those of Mao and are not obvious in view of Mao.

Summary- structural, chemical and biological differences between implants of Mao and those of the present invention

Accordingly, many differences exist in structural and chemical characteristics and biological properties between the implants disclosed in the Mao and those recited in the subject claims. For examples, polymers of the implants of the present invention: (a) lack a phosphate group present in the polymers of Mao; (b) contain 20-40% haloperidol, which confers decreasing release rate with increasing drug percentage; (c) are manufactured by solvent casting and compression molding; (d) exhibit steady-state release for 5 months or more; and (e) are removable.

Applicants respectfully assert that the Examiner's rationale for rejecting the subject claims has depended on the erroneous understanding that the implants disclosed in the Mao differ from those of the subject invention only in the drug percentage, as alleged on page 3, first full paragraph of the October 19, 2006 Office Action.

Applicants therefore respectfully request that the rejection be withdrawn.

Lack of enabling disclosure for haloperidol-containing implants in Mao

Regarding haloperidol, as mentioned hereinabove, the Examiner alleged that Mao disclosed the use of any antipsychotic drugs (e.g. clozapine, haloperidol, and risperidone) with the proposed implants.

In response, Applicants have previously pointed out to the Examiner that haloperidol is disclosed as part of a very large list encompassing hundreds of different active compounds (of the 129 items listed, many items are actually classes of compounds, each of which may contain several to dozens of known active compounds), without providing any guidance as to which of the compounds would likely work in the implants disclosed therein, or without providing enablement of any of the compounds on the list.

In response to Applicants' arguments, the Examiner alleged in the Advisory Action that the listing of antipsychotic drugs is limited to three- clozapine, risperidone, and haloperidol, and thus does not represent a "laundry list."

Applicants respectfully disagree. The number of antipsychotic drugs disclosed in Mao does not change the fact that Mao provides no guidance as to which of the hundreds of total compounds listed would likely work in the implants disclosed therein and provides no enablement of combining any of the compounds in the list with the implants disclosed in Mao. Further, a person skilled in art knew that a mere suggestion to combine a drug with a particular polymer does not provide enablement in the absence of data for the particular drug, as shown, for example, in the teaching of the subject specification that thiothixene behaves completely different from haloperidol in implants of the present invention:

> "Inclusion of haloperidol in the drug delivery system actually increases the stability of the drug delivery system. Thus, the higher the concentration of haloperidol, the more extended the period of release. This increase in stability does not occur with all drugs. In fact, other antipsychotic drugs such as thiothixene decreased stability and the period of release of the drug delivery system when drug concentrations were increased" (page 9, lines 11-16).

Thus, Mao does not provide an enabling disclosure of a combination of haloperidol with the implants disclosed therein.

Applicants therefore respectfully request that the rejection be withdrawn.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

DRAFT

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